UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,195	11/14/2003	Joffre B. Baker	GHDX-005	5745

24353 7590 02/25/2010

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
02/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,195	BAKER ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2009 and 07 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,35-38,40-47,51,52,59,60,62,64 and 66-83* is/are pending in the application.

4a) Of the above claim(s) *40 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,35-38,41-47,51,52,59,60,62 and 66-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/2009; 12/7/2009; and 2/17/2010*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 3, 2009 and December 7, 2009. This action is made FINAL.

Claims 31, 35-38, 40-47, 51-52, 59-60, 62, 64, and 66-83 are currently pending.

Claims 31, 38, 41, 51, 52, and 60 have been amended.

Claims 66-83 have been amended.

Claims 40 and 64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 23, 2006.

Declarations

2. The declaration under 37 CFR 1.132 filed December 3, 2009 by Joffre Baker and Steve Shak are insufficient to overcome the enablement rejection set forth in the last Office action. A detailed explanation is presented below in paragraph 6.

Withdrawn Objections

3. The objections made in section 2 of the Office Action of June 3, 2009 are withdrawn in view of the Applicants arguments and the amendments made to the claims.

Withdrawn Rejections

4. The rejections made under 35 USC 112 2nd paragraph in section 3 of the Office Action of June 3, 2009 are withdrawn in view of the amendments made to the claims.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection has been modified based on the claim amendments:

Claims 31, 35-38, 41-47, 51-52, 59-60, 62, and 66-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Nature of the Invention

Claims 31 is drawn to a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an inhibitor of ErbB1 activation. Claim 31 comprises (a) assaying a normalized level of a predictive RNA transcript in a sample comprising ErbB1 expressing colon cancer cells obtained from said patient wherein the predictive RNA transcript is the transcript of laminin gamma 2 (LAMC2); (b) analyzing the normalized level of the LAMC2 transcript; and (c) predicting the likelihood of response of the patient to treatment with an inhibitor of ErbB1 activation based on the normalized level of the LAMC2 transcript, wherein an increased normalized level of LAMC2 RNA transcript correlates with resistance of the colon cancer to treatment with the inhibitor of ErbB1 activation, wherein the inhibitor of ErbB1 activation binds to ErbB1 and is erlotinib, cetuximab, or gefitinib. Thus the nature of the invention requires the knowledge of a reliable association between the level of LAMC2 in a sample and how a patient will respond to treatment with an ErbB1 inhibitor, specifically erlotinib, cetuximab, or gefitinib.

Claim 66 is drawn to a method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an inhibitor of ErbB 1 activation. Claim 66 comprises (a) assaying a normalized level of a predictive RNA transcript in a sample comprising ErbB 1 expressing colon cancer cells obtained from said patient, wherein the predictive RNA transcript is the transcript of laminin gamma 2 (LAMC2); (b) analyzing the normalized level of the LAMC2 transcript; and (c) predicting the likelihood of response of the patient to treatment with the inhibitor of ErbB 1 activation based on the normalized level of the LAMC2 transcript, wherein an

increased normalized level of LAMC2 RNA transcript correlates with resistance of the colon cancer to treatment with the inhibitor of ErbB 1 activation, wherein the inhibitor of ErbB 1 activation is a monoclonal antibody that binds to ErbB 1. Thus the nature of the invention requires the knowledge of a reliable association between the level of LAMC2 in a sample and how a patient will respond to treatment with any monoclonal antibody that binds to ErbB1.

Scope of the Claims:

Claim 31 is broadly drawn to method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an inhibitor of ErbB1 activation wherein the inhibitor of ErbB1 activation binds to ErbB1 and is erlotinib, cetuximab, or gefitinib.

Claim 66 is broadly drawn to method for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with an inhibitor of ErbB1 activation wherein the inhibitor of ErbB1 activation ANY monoclonal antibody that binds to ErbB1. Claim 67 further states that the monoclonal antibody is cetuximab.

Teachings in the Specification and Examples:

The specification (page 25) teaches that EGFR (also known as ErbB1) is known to be active in several tumor types such as breast, colon, and head and neck cancers. The specification also teaches that several ErbB1 inhibitors are promising drug candidates for the treatment of ErbB1 expressing cancers. The specification further teaches the following ErbB1 inhibitors: (i) Iressa (gefitinib) is a small synthetic

quinazoline that competitively inhibits the ATP binding site of ErbB1 and has been in Phase III clinical trials for the treatment of non-small-cell lung carcinoma; (ii) [agr]cyano-[bgr]methyl-N-[(trifluoromethoxy)phenyl]-propenamide (LFM-A12) has been shown to inhibit the proliferation and invasiveness of ErbB1 positive human breast cancer cells; (iii) Cetuximab is a monoclonal antibody that blocks the ErbB1 and ErbB1 -dependent cell growth that is currently being tested in phase III clinical trials; and (iv) Tarceva™ (erlotinib) which has shown promising indications of anti-cancer activity in patients with advanced ovarian cancer, and non-small cell lung and head and neck carcinomas.

The specification teaches (Example 2) that twenty-three colon adenocarcinoma patients in all were studied using a 192-gene assay. Following treatment with an unspecified ErbB1 inhibitor, three patients were determined to have had a partial response, five to have stable disease, and fifteen to have progressive disease. Table 3 shows the results obtained using the partial response criterion. LAMC2 was found to be over expressed. Specifically LAMC2 had a negative response and a p value of 0.0357. Here the term "negative" indicates that greater expression of the gene decreased likelihood of response to treatment with ErbB1 inhibitor, and "positive" indicates that increased expression of the gene increased likelihood of response to ErbB1 inhibitor (page 28). Table 4 shows the results analysis of colon cancer patient data using clinical benefit criteria. Here there is no data provided for LAMC2. Further with respect to claim 60 Table 4 shows that CD44v6 had a negative response and a p value of 0.0047.

In the instant case the specification does not teach which ErbB1 inhibitors were used. However it is noted for the record that on April 17, 2008 the Applicants have

submitted a declaration by Joffre B. Baker, PhD stating that the patients were treated with an ErbB1 inhibitor selected from erlotinib, gefitinib, cetuximab, EMD72000, and AEE788. Dr. Baker states that the results presented in tables 3 and 4 were the result of treatment with these ErbB1 inhibitors. Then on December 3, 2009 the Applicants submitted two more declarations by Joffre B. Baker, PhD and Steve Shak M.D. stating that 15 patients were treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. The declaration further states that the three partial responders were treated with EMD72000 alone.

Thus the data presented in Table 3 is based on 15 patients treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. Based on the declarations it appears that erlotinib and gefitinib were not used in the study. Therefore the specification does not provide enablement for predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with erlotinib or gefitinib.

Additionally the declaration by Steven Shak MD refers to a graph showing the LAMC2 mRNA level for each of the patients (See Exhibit B). The declaration states that the 23 patients were grouped into either non partial responders (No PR) or partial responders (Yes PR). Each circle represents a patient. The graph has been fully considered and first of all it is noted that there are only 21 circles present, therefore 2 patients are unaccounted for. As shown in Exhibit B the 3 partial responders had LAMC2 values ranging between approximately 3.1-5.25 whereas the 18 non responders had LAMC2 values ranging between approximately 3.2-7.5. Here it is noted that there

is substantial overlap between the two groups. In fact 10 of the 18 non responders had LAMC2 values that fell within the 3.1-5.25 range. Based on this information it does not appear that one of skill in the art could accurately predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with either of these two drugs since 10 of the non responders would have been predicted to respond based on their LAMC2 levels.

State of the Art and the Unpredictability of the Art:

Further the art of determining if erlotinib, cetuximab, gefitinib, and other monoclonal antibody that binds to ErbB1 will each be less effective in patients with increased LAMC2 levels is highly unpredictable. The post filing date art of Giaccone teach six EGFR (also known as ErbB1) inhibitors (Iressa (gefitinib), Tarceva (erlotinib), lapatinib, cenertinib, ZD6474, and AEE788). Giaccone additionally teaches that each of these drugs has a different mechanism in which it acts on EGFR receptor. For example Iressa (gefitinib) and Tarceva (erlotinib) inhibit the tyrosine kinase of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR. These teachings are relevant to point out because the Applicants have not even test erlotinib or gefitinib or shown that the data that they do have could be extrapolated in any monoclonal antibody. In the absence of a clear showing of an association between increased LAMC2 mRNA levels and a clinically beneficial response to each of the drugs erlotinib, cetuximab, or gefitinib or a representative number of monoclonal antibodies that bind to ErbB1 it is highly

unpredictable as to whether LAMC2 mRNA levels can be used to predict the likelihood of a beneficial response to these drugs particularly since each of the claimed drugs is present in a different class of ErbB1 inhibitors and has a different mechanism in which it acts on the ErbB1 receptor.

Quantity of Experimentation:

The specification asserts that patients diagnosed with colon cancer with elevated levels of LAMC2 are less likely to respond to a treatment with an ErbB1 inhibitor. However the examples in the specification were only conducted using cetuximab and EMD 72000. Based on the data presented in the specification and declarations that have been filed it is unpredictable if the claimed method works cetuximab and EMD 72000 and since erlotinib, gefitinib, and a representative number of monoclonal antibodies that bind to ErbB1 have not even been tested its unpredictable if the claimed method will work for this inhibitors. Thus further experimentation would be required. For example, such experimentation may involve treating colon cancer patients with different types of ErbB1 inhibitors such as erlotinib, cetuximab, gefitinib, and a representative number of different monoclonal antibodies that bind to ErbB1 and conducting multiple gene expression assays to determine the expression levels of LAMC2. Further these patients would have to be monitored to determine disease progression. Such random, trial by error experimentation is considered to be undue. The specification has provided only an invitation to experiment.

Conclusions:

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response to Arguments

6. Regarding the enablement rejection the Applicants state that the inhibitors of ErbB1 activation erlotinib, cetuximab, and gefitinib recited in claim 31 and a monoclonal antibody recited in claim 66 all have a common function in that they inhibit the very first step required for ErbB1 dependent cell signaling. They further cite references which state how these different inhbitors work by inactivating ErbB1. Further they argue that there is no need to separately establish the level of LAMC2 mRNA in subjects showing a benefical response to erlotinib, cetuximab, and gefitinib because they are all of the same class in that they all function to inhibit activiatio of ErbB1 by binding to ErbB1.

This argument has been fully considered but is not persuassive. The prior art of Baselga (The Oncologist 2002 Vol 7 pages 2-8), cited by applicants, states that are 5 different classes of compounds that target EGFR (mAbs, bispecific abs, TKIs, recombinant vaccines, and antisense oligonucleotides). With respect to the TKIs there are 4 different sublasses of drugs. While they may all have the common function of inhibiting activation of ErbB1 they are not regarded in the art as bieng in the same class

of compounds. Further it is noted that Baselga teaches that while cetuximab causes an increase in the expression of the cell cycle inhibitor $p27^{KIPI}$ –cyclin dependent kindase 2 complexes that prevent cells from exiting the G1 phase of the cell cylce, it also has been shown to induce apoptosis in some cells lines and to inhibit the production of angiogenic factors as well as metasis. Additionally gefitinib (EGFR-TKI ZD1839) in addition to reducing cell proliferation gefitinib also induces cell cycle arrest, increasese apoptosis, has antiangiogenic activity, and antimetastic properties (pages 5, col 2). Therefore while each of these drugs may have common properties they are distinct from one another because of their additional properties. Further the disclosure of a single monoclonal antibody (cetuximab) in the specification and data based on two monoclonal antibodies (cetuximab and EMD 27000) is not representative of the class of monoclonal antibodies that bind to ErbB1 and inhibit activation of ErbB1

Regarding the declarations it is noted that on April 17, 2008 the Applicants submitted a declaration by Joffre B. Baker, PhD stating that the patients were treated with an ErbB1 inhibitor selected from erlotinib, gefitinib, cetuximab, EMD72000, and AEE788. Then on December 3, 2009 the Applicants submitted two more declarations by Joffre B. Baker, PhD and Steve Shak M.D. stating that 15 patients were treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. The declaration further states that the three partial responders were treated with EMD72000 alone. The declarations and the Applicants arguments regarding the declaration have been fully considered but are not persuasive.

In view of the most recent declarations the data presented in Table 3 is based on 15 patients treated with the ErbB1 inhibitor EMD 72000 and 8 patients were treated with cetuximab, with or without chemotherapy. Based on the declarations it appears that erlotinib and gefitinib were not used in the study. For this reason the declaration is not persuasive in establishing that it is possible to predicting the likelihood that a human colon cancer patient will exhibit a clinically beneficial patient response to treatment with erlotinib or gefitinib or any other monoclonal antibody which binds to ErbB1 and inhibits activation.

The declaration of Steven Shak MD refers to a graph showing the LAMC2 mRNA level for each of the patients (See Exhibit B). The declaration states that the 23 patients were grouped into either non partial responders (No PR) or partial responders (Yes PR). Each circle represents a patient. The graph has been fully considered and first of all it is noted that there are only 21 circles present, therefore 2 patients are unaccounted for. As shown in Exhibit B the 3 partial responders had LAMC2 values ranging between approximately 3.1-5.25 whereas the 18 non responders had LAMC2 values ranging between approximately 3.2-7.5. Here it is noted that there is substantial overlap between the two groups. In fact 10 of the 18 non responders had LAMC2 values that fell within the 3.1-5.25 range. Based on this information it does not appear that one of skill in the art could accurately predict the likelihood that a human colon cancer patient will exhibit a clinically beneficial response to treatment with either of these two drugs since 10 of the non responders would have been predicted to respond based on their LAMC2 levels.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634